REMARKS

Prior to the present amendment, claims 1-6, 9-18, and 21-67 were pending in the present application. All claims withdrawn from consideration have been canceled without prejudice or disclaimer therein and Applicants reserve the right to pursue these claims in continuing applications that claim priority to the present application. Therefore, by the present amendment, claims 1-6, 9, 11-14, 16-18, 28, 62, 67-69 are pending in the present application. Support for newly added claim 68 and 69 can be found on page 16, paragraph 74.

Claim 11-14 and 23-26 stand rejected under 35 U.S.C. 112 for allegedly being indefinite. Claim 21 stands rejected for allegedly failing to comply with the written description requirement. Claims 1, 2, 9, 11-14, 23-26, 28, 62 and 67 stand rejected under 35 U.S.C. 102(e) for being allegedly anticipated by U.S. Patent Publication 2004/0259156 to Zhu ("Zhu"). Claims 1-5, 9, 11-14, 16-17, 23-26, 28, 62, and 67 stand rejected under 35 U.S.C. 103(a) for being allegedly rendered obvious by Rockwell et al., Molecular and Cellular Differentiation, 3(4): 315-335 (1995) ("Rockwell") in view of Ciardiello et al. Clinical Cancer Research, 6:3739-3747 (September 2000) ("Ciardiello") and Siemeister et al. Cancer and Metastasis Reviews 17:241-248 (1998) ("Siemeister") and U.S. Patent No. 5,530,101 to Queen ("Queen").

Rejection of Claims 11-14 and 23-26 under 35 U.S.C. 112

Claims 11-14 and 23-26 stand rejected under 35 U.S.C. 112 for lacking antecedent basis for the limitation "the antibody." Claims 11-14 have been amended to clarify that the antibody refers to the VEGFR antibody of claim 1, the EGFR antibody of claim 1, or both the VEGFR antibody and the EGFR antibody of claim 1. As such, Applicants submit that claims 11-14 have proper antecedent basis. Claims 23-26 have been canceled as they are duplicative of claims 11-14 and therefore the rejection of claims 23-26 is rendered moot.

Rejection of Claim 21 Under 35 U.S.C. 112

Claim 21 stands rejected under 35 U.S.C. 112 for allegedly containing new matter. Claim 21 has been canceled rendering this rejection moot.

Priority Claim

Applicants point out that the priority of the present application was amended in the supplemental amendment of February 1, 2005.

Rejection of Claims 1, 2, 9, 11-14, 23-26, 62, and 67 Under 102(e)

According to the Examiner, Zhu teaches a method of inhibiting or reducing tumor growth by administering an antigen-binding protein that binds flt-1 and EGFR and blocks ligand binding. However the passage cited by the Examiner (in addition to any other part of the reference) does not describe inhibiting binding of a ligand to EGFR. Rather the reference only describes blocking ligand binding to KDR and/or flt-1, both of which are VEGFR receptors. As such, Zhu does not teach a specific limitation of claim 1—namely administering an EGFR antibody or functional equivalent thereof that inhibits binding of a ligand thereto. In any event, in order to clarify that claim 1 is directed to administering of at least two separate antibodies, Applicants have amended claim 1 to recite administration of a VEGFR antibody and a separate EGFR antibody. Clearly, Zhu does not teach or suggest administration of two separate antibodies since the very point of Zhu is description of a single antibody that has two different antigen-binding sites. As such, Applicants submit that claim 1 (and all claims that depend therefrom) are not anticipated by Zhu and Applicants request withdrawal of this rejection.

Similarly, claim 62 has been amended to recite a kit comprising an EGFR antibody and a separate VEGFR antibody. Notwithstanding whether the "inhibiting tumor growth" is read into the claim as a positive limitation, the claim still recites an EGFR antibody that inhibits binding of a ligand to an EGFR. As stated above, Zhu does not describe an EGFR antibody that inhibits binding of a ligand to EGFR. Such inhibition is only described with respect to VEGFR. Further, Zhu does not describe a kit having at least two separate antibodies. As such, Zhu does not teach each and every element of claim 62 and Applicants request withdrawal of this rejection.

Rejection of Claims 1-5, 9, 11-14, 16-17, 23-26, 28, 62, and 67 Under 35 U.S.C. 103(a) by Rockwell in View of Ciardiello and Siemeister and Queen

Applicants submit that a *prima facie* case of obviousness has not been made since there is no motivation to combine the teachings of the Rockwell article with the teachings of

the Ciardiello article to produce the claimed invention-*i.e.* a method of inhibiting tumor growth by administering a combination of a VEGFR antibody and an EGFR antibody.

It is true that Ciardello claims an alleged synergistic effect upon administration of an antisense VEGF oligonucleotide with an EGFR antibody. However, this does not mean that is obvious to administer a VEGFR antibody with an EGFR antibody given the disclosure of Rockwell. In order for there to be a prima facie case of obviousness, there must be some motivation or suggestion to even combine the teachings of Ciardello with the teachings of Rockwell. Applicants submit that there is no such motivation.

Rockwell describes an EGFR antibody and a VEGFR antibody, but there is not even the slightest suggestion that these two antibodies should be used together in a combination therapy. The Examiner cites to the passage in Rockwell that states that there is mounting preclinical and clinical data that combines therapies may more efficacious than a single agent. As Applicants pointed out in their Response of June 22, 2004, a review of the complete citation makes it clear that the combination therapies referred to are a combination of a single antibody and a chemotherapeutic agent. Specifically, Rockwell states "[t]he possibility exists that the generation of neutralizing antibodies to many of these [protein tyrosine kinase] receptors will also find utility as anti-cancer agents alone or in combination with chemotherapeutics ." Rockwell (1995) at page 327-28 (*emphasis added).* The experimental data described is C225 in combination with chemotherapeutics such as cisplastin and doxorubicin. There is absolutely no teaching or suggestion in Rockwell to combine an anti-VEGFR antibody with an anti-EGFR antibody according to the present claims.

Even if a *prima facie* case of obviousness were established (which Applicants are obviously not conceding based on the above arguments), Applicants submit that the claimed invention yields unexpected results. Specifically, Applicants submit herewith a Declaration under 37 C.F.R. 1.132 by Dr. James R. Tonra of ImClone Systems Incorporated that describes an experiment that compares administration of an EGFR antibody alone, a VEGFR antibody alone, and a combination of an EGFR antibody and a VEGFR antibody. As shown from the test results, the dose of the EGFR antibody causing a 50% inhibition of tumor growth (defined as a % T/C value of 50 or ED50) is 1.78 mg/kg. The dose of the VEGFR antibody causing a 50% inhibition in tumor growth is 16.60 mg/kg. The dose of combination treatment of these two antibodies at a ratio of 8 mg/kg of the VEGFR antibody for each 1 mg/kg of the EGFR antibody is 0.86 mg/kg.

A combination index (CI) was determined to evaluate the effect of the combination treatment. A CI=1 indicates that the effect of the two treatments administered together is equal to the sum of the effects of each treatment administered alone (*i.e.* an additive effect). A CI greater than 1 indicates that the effect of the two treatments administered together is less than the sum of the effects of each treatment administered alone (*i.e.* a sub-additive effect). A CI less than 1 indicates that the effects of the two treatments administered together is greater than the sum of the effects of each treatment administered alone (*i.e.* a synergistic effect). As summarized by the data presented in the declaration, the CI of the combination treatment of an EGFR antibody and a VEGFR antibody was 0.1, which is significantly less than 1, indicating a synergism between the EGFR antibody and the VEGFR antibody.

Based on these results, not only does combining an EGFR and a VEGFR antibody lead to greater inhibition of tumor growth than either antibody administered alone (as seen in Figure 1 of the Declaration), but less of each antibody is needed to achieve 50% inhibition in tumor growth when given in combination than would be expected from simply adding together the effects of the two separate treatments. As such, Applicants submit that the present claims yield unexpected results and are not rendered obvious by the Rockwell patents in view of Ciardiello, Siemeister, and Queen and Applicants request withdrawal of this rejection.

CONCLUSION

It is respectfully submitted that the present application is now in condition for allowance, as all outstanding issues have been addressed. The Examiner is invited to contact Applicants' representative to discuss any issue that would expedite allowance of the subject application.

Any fees for extension(s) of time or additional fees are required in connection with the filing of this response, such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and the Commissioner is authorized to charge any such required fees or to credit any overpayment to Kenyon & Kenyon's Deposit Account No. 11-0600.

Respectfully submitted,
KENYON & KENYON

Dated: September 29, 2005

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